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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,245	10/27/2003	Timothy A. Morris	1133.005US2	4050

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EXAMINER	
GRUN, JAMES LESLIE	
ART UNIT	PAPER NUMBER
1641	
MAIL DATE	DELIVERY MODE
03/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/694,245	MORRIS, TIMOTHY A.	
	Examiner	Art Unit	
	JAMES L. GRUN	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *22 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,11-20,22-26,29,30 and 49-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,11-20,22-26,29,30 and 49-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 22 February 2008 has been entered. Claims 2, 7-10, 21, 27, 28, and 31-48 have been cancelled. Claims 1, 3-6, 11-20, 22-26, 29, 30, and 49-52 remain in the case.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is objected to and claims 1, 3-6, 11-20, 22-26, 29, 30, and 49-52 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons similar to those of record in the prior rejection of the similar subject matter of these claims as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification, as originally filed, does not provide written description support for an antiserum detection reagent having a ratio of IC_{50} for fibrinogen to that of des-arginine fibrinopeptide B or fibrinopeptide B of at least 0.34, or about 0.5, as is now claimed. The specification, as originally filed, also does not provide written description support for an antiserum detection reagent having a ratio of IC_{50} for des-arginine fibrinopeptide B to that of fibrinopeptide B of about 0.75 as is now claimed. The specification, as originally filed, does not provide written description support for an antiserum detection reagent that binds to des-arginine fibrinopeptide B and/or fibrinopeptide B and does not cross-react with fibrinogen with an IC_{50} ratio of at least 0.34 as is now claimed. Applicant discloses that a single polyclonal antiserum comprising a single bleeding of a single rabbit (i.e. R4097, bleed I3) elicited by immunization with human fibrinopeptide B was selected as having the "best reactivity profile" for use and that this antiserum as a whole: had a cross-reactivity with des-arginine fibrinopeptide B which was 75% of that with fibrinopeptide B as determined by IC_{50} values in a competitive enzyme-linked immunosorbent assay in which the competitive inhibition of the binding of the antibody to human fibrinopeptide B by the peptides was determined and related in a particular fashion (i.e. the IC_{50} for fibrinopeptide B divided by the IC_{50} for des-arginine fibrinopeptide B was 0.75); reacted with fibrinogen better than with fibrinopeptide B (i.e. the IC_{50} for fibrinogen (2.3 nM) divided by the IC_{50} for fibrinopeptide B (6.7 nM) was 0.34) (see e.g. pages 27-28 and 40-41). The instantly claimed invention also does not set forth the relevant comparison for determining the difference in IC_{50} values. Although one of skill in the art might realize from reading the

disclosure that antibodies binding with cross-reactivities as are now claimed are useable in the invention, such possibility of use does not provide explicit or implicit indication to one of skill in the art that an antibody with such cross-reactivity ranges as are now claimed was originally contemplated as part of applicant's invention, particularly since applicant does not disclose such a reactivity profile for the antibody and exemplifies a single polyclonal antibody which meets only specific limits of the ranges as are now claimed, and such possibility of use does not satisfy the written description requirements of 35 U.S.C. § 112, first paragraph. Note that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement. Applicant is requested to direct the Examiner's attention to specific passages where support for these newly recited limitations can be found in the specification as filed or is required to delete the new matter.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115). However, the reproducibility of an antiserum with properties as claimed would seem unknown and unpredictable in view of the disclosure that only a single bleeding from a single immunized rabbit, selected as best for use, had properties close to those as claimed. Absent further written description and guidance, one would have no assurance of predictably obtaining additional polyclonal antibody populations with the relevant properties for use. The variability of polyclonal antisera binding properties after immunization with fibrinopeptide B is clearly shown in Wilner et al. (Biochem. 18: 5078, 1979). Again, note that even an enabling disclosure for the preparation and use of only a few analogs of a product does not enable all possible analogs

where the characteristics of the analogs are unpredictable. See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* (18 USPQ 2d 1027 (CAFC 1991)).

Applicant's arguments filed 22 February 2008 have been fully considered but they are not deemed to be persuasive.

Notwithstanding applicant's assertions to the contrary, applicant's amendments have not obviated rejections under this statute for the reasons set forth above.

Applicant urges that the specification describes and enables the invention as claimed because the skill in the art is high and applicant need not describe every detail of the invention. This is not found persuasive for the reasons of record and as set forth above, specifically because the invention as is now claimed lacks sufficient written description in the specification as originally filed and because the reproducibility of an antiserum with properties as claimed would seem unknown and unpredictable in view of the disclosure that only a single bleeding from a single immunized rabbit, selected as best for use, had properties close to those as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-20, 22-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 11 and claims dependent thereupon, the method is not clear because it is not clear how complex is present in the sample. The examiner would suggest --contacted-- sample in step (b). In claim 11 and claims dependent thereupon, the method is also not clear because it

is not clear how detection of the presence of complex relates to later claimed peptide concentrations.

Applicant's arguments filed 22 February 2008 have been fully considered but they are not deemed to be persuasive.

Notwithstanding applicant's assertions to the contrary, applicant's amendments have not obviated rejections under this statute for the reasons set forth above.

Applicant urges that the presence of complexes can be quantitated as is routine in the art. This is not found persuasive because merely detecting presence is claimed and, although claims are interpreted in light of the disclosure, limitations from the specification are not imported into the claims unnecessarily. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). See also *In re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) ("During patent examination the pending claims must be interpreted as broadly as their terms reasonably allow.... The reason is simply that during patent prosecution when claims can be amended, ambiguities should be recognized, scope and breadth of language explored, and clarification imposed.... An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process.").

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1, 3-6, 11-17, 22-26, 29, 30, 49, 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kudryk et al. (US 5,876,947), in view of Galfrè et al. (Meth. Enz. 73: 3, 1981) and Eckhardt et al. (J. Clin. Invest. 67:809, 1981).

Claims 1, 3-6, 11-17, 22-26, 29, 30, 49, 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kudryk et al. (WO 99/05176), in view of Galfrè et al. (Meth. Enz. 73: 3, 1981) and Eckhardt et al. (J. Clin. Invest. 67:809, 1981).

Kudryk et al. (US '947) disclose monospecific antibodies which bind to an epitope as present in fibrinogen, fibrinopeptide B, or des-Arg fibrinopeptide B (SEQ ID NO:1), contained in its entirety by all of the instantly claimed sequences SEQ ID NOs:1-6, without regard to whether the C-terminal Arg residue has been cleaved from the fibrinopeptide B or whether the N-terminal residue is glutamine or pyroglutamic acid, and which is specifically exemplified by a monoclonal antibody produced by the P10 hybridoma, deposited as ATCC Accession No. HB-12398 (e.g. cols. 3-6, 7, 23). As fibrinogen contains 2 moles of fibrinopeptide B (see e.g. col. 21), such an antibody as suggested in the reference would implicitly have the IC_{50} ratios as instantly claimed. Antigen binding fragments Fab, $F(ab')_2$, or Fv of the monospecific antibodies, including that produced by the P10 hybridoma, are also disclosed. The antibody or fragment can be attached to a substrate or detectably labeled by conjugation to a detectable moiety (see e.g. cols. 4, 11-12) for use in immunoassay detection of antigen and diagnosis of the presence or probability of thrombogenesis or atherogenesis in a subject (see e.g. cols. 3-6, 13, 15, 22).

Antibodies can be elicited by conjugating a peptide via a Cys residue to a carrier such as keyhole limpet hemocyanin (e.g. col. 9). The antibodies can be provided in kits (see e.g. col. 16).

Kudryk et al. (WO '176) disclose monospecific antibodies which bind to an epitope as present in fibrinogen, fibrinopeptide B, or des-Arg fibrinopeptide B (SEQ ID NO:1) without regard to whether the C-terminal Arg residue has been cleaved from the fibrinopeptide B or whether the N-terminal residue is glutamine or pyroglutamic acid, and which is specifically exemplified by a monoclonal antibody produced by the P10 hybridoma (e.g. pages 5-6, 10, 12) . As fibrinogen contains 2 moles of fibrinopeptide B, such an antibody as suggested in the reference would implicitly have the IC_{50} ratios as instantly claimed. Antigen binding fragments Fab, $F(ab')_2$, or Fv of the monospecific antibodies, including that produced by the P10 hybridoma, are also disclosed. The antibody or fragment can be attached to a substrate or detectably labeled by conjugation to a detectable moiety (see e.g. page 5) for use in immunoassay detection of antigen and diagnosis of the presence or probability of thrombogenesis or atherogenesis in a subject (see e.g. pages 6-8, 22, 31-32). Antibodies can be elicited by conjugating a peptide via a Cys residue to a carrier such as keyhole limpet hemocyanin (e.g. page 13). The antibodies can be provided in kits (see e.g. page 23).

In contrast to the invention as instantly claimed, Kudryk et al. (US '947) or Kudryk et al. (WO '176) do not specifically teach antiserum for use in their methods, multiple determinations of fibrinopeptide levels in the same patient, or threshold levels as instantly claimed.

Galfrè et al. teach that large amounts of monoclonal antibody can be produced by growing hybridomas as tumors in mice and collecting body fluids, particularly serum, from the tumor-bearing mice (see e.g. pages 41-45).

Eckhardt et al., inter alia, teach radioimmunoassay for desarginine fibrinopeptide B in biological fluid samples using oligoclonal antibodies selected for reactivity for this antigen. The reference suggests the determination of fibrinopeptide B as an indicator of fibrin II formation and that the formation of fibrin II determines the occurrence of thrombosis (page 809, col. 2). Multiple determinations of levels in the same patient over time to monitor the course of fibrinogenolysis treatment effects are taught.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have substituted antiserum in the methods of Kudryk et al. (US '947) or Kudryk et al. (WO '176) in view of the direct suggestion in the reference of Galfrè et al. to produce large quantities of monoclonal antibodies in mice by inducing solid tumors and collecting serum therefrom. Determinations of threshold values indicative of disease would have been obvious to one of ordinary skill in the art since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233. It would have been further obvious to one of ordinary skill in the art at the time the instant invention was made to have performed multiple determinations on a patient with the methods of Kudryk et al. (US '947) or Kudryk et al. (WO '176), as modified, to determine the effects of treatments affecting fibrinogenolysis in view of the teachings of Eckhardt et al. regarding the detectable changes in plasma sample concentrations of fibrinopeptide B after such treatments.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 1, 3-6, 11-17, 22-26, 29, 30, 49, 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kudryk et al. (US 5,876,947), in view of Eckhardt et al. (J. Clin. Invest. 67:809, 1981) for reasons of record in the prior rejection of the similar subject matter of these claims.

Claims 1, 3-6, 11-17, 22-26, 29, 30, 49, 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kudryk et al. (WO 99/05176), in view of Eckhardt et al. (J. Clin. Invest. 67:809, 1981) for reasons of record in the prior rejection of the similar subject matter of these claims.

Applicant's arguments filed 22 February 2008 have been fully considered but they are not deemed to be persuasive.

Notwithstanding applicant's assertions to the contrary, applicant's amendments have not obviated rejections under this statute for the reasons set forth above.

Applicant urges that the P10 monoclonal antibody, as specifically exemplified in the references of Kudryk et al., does not have the binding reactivity with fibrinogen as is now claimed. This is not found persuasive because the disclosure of the reference is considered as a whole and is not limited to that which is specifically exemplified. As set forth, Kudryk et al. disclose monospecific antibodies which bind to an epitope as present in fibrinogen, fibrinopeptide B, or des-Arg fibrinopeptide B (SEQ ID NO:1) without regard to whether the epitope is in native protein or whether the C-terminal Arg residue has been cleaved from the fibrinopeptide B or whether the N-terminal residue is glutamine or pyroglutamic acid. As fibrinogen contains 2 moles of fibrinopeptide B (see e.g. col. 21 in US '947), such an ideal antibody of the invention would implicitly have the IC_{50} ratios as instantly claimed.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-6, 11-14, 18-20, 22-26, 29, 30, 49, 51, and 52 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,673,561, in view of Kudryk et al. (US 5,876,947 or WO 99/05176) for reasons of record.

Applicant's arguments filed 22 February 2008 have been fully considered but they are not deemed to be persuasive.

Notwithstanding applicant's assertions to the contrary, no proper terminal disclaimer is of record.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/J. L. G./
James L. Grun, Ph.D.
Examiner, Art Unit 1641
March 27, 2008

/Long V Le/
Supervisory Patent Examiner, Art Unit 1641